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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,697	07/25/2001	Nicholas C. Nicolaides	MOR-0040	5193
23377	7590	08/10/2005	EXAMINER	
WOODCOCK WASHBURN LLP ONE LIBERTY PLACE, 46TH FLOOR 1650 MARKET STREET PHILADELPHIA, PA 19103			LUCAS, ZACHARIAH	
			ART UNIT	PAPER NUMBER
			1648	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/912,697	Applicant(s) NICOLAIDES ET AL.	
	Examiner Zachariah Lucas	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 June 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,14-25,27,38,43 and 46-48 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) 1,14-25,27,38,43 and 46-48 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>5-9-05</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Status of the Claims

1. Claims 1, 14-25, 27, 38, 43, and 46-48 are pending and under consideration in the application.
2. In the prior action, mailed on March 22, 2005, claims 1, 3, 14-25, 27, 38, and 42-50 were pending and rejected. In the Response filed on June 27, 2005, the Applicant amended claims 1, 25, 38, 43, and 48; and cancelled claims 3, 42, 44-45, 49, and 50.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on May 9, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. **(Prior Rejection- Withdrawn)** Claims 1, 14-25, 27, 38, 43, and 46-48 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the application does not provide written description support claims drawn to

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inventions relating to any mismatch repair gene alleles. In view of the amendment of the claims limiting them to embodiments wherein the mismatch repair gene allele is one of PMS2-134 or PMSR3, the rejection is withdrawn.

6. **(Prior Rejection- Withdrawn)** Claims 1, 14-25, 27, 38, 43, and 46-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for bacteria and methods of producing such, comprising one of the dominant negative alleles PMS2-134 or PMSR3, does not reasonably provide enablement for methods or bacteria involving any dominant negative repair gene allele. In view of the limitation of the claims to the embodiments indicated to be enabled, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. **(Prior Rejection- Maintained)** Claims 1, 3, 15, 27, and 38, and 42 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over Nicolaides 1 (U.S. Pre-Grant Publication 2002/0068284) further in view of the teachings of Iris (U.S. 6,221,585) and Morris (J Infect Dis 171: 954-60). Claims 3 and 42 have been cancelled from the application. The rejection is therefore withdrawn from these claims. The Applicant traverses the rejection of the remaining claims by asserting 1) that the Iris fails to provide motivation for the creation of hypermutable

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bacteria, and 2) the Morris reference fails to provide motivation for the creation of multi-antibiotic resistant bacteria.

The Applicant asserts that the Iris reference fails to provide motivation for the making of hypermutable bacteria because the reference requires the homogenization, not the random mutation of, nucleic acids to be compared. While the Examiner agrees that the Iris reference itself fails to provide such a motivation, the reference is concerned with the identification of identifying genotypes associated with target phenotypes. Nicolaides I teaches the use of the described mismatch repair deficient cells to generate cells with phenotypes of interest. Thus, while Iris provides a reason that those in the art would want to create and identify genotypes associated with target phenotypes, it is the teachings of Nicolaides I that provides the motivation to use mismatch repair. The Applicant's first argument in traversal is therefore not found persuasive.

With respect to the Morris reference, the Applicant asserts that the reference fails to provide motivation for the creation of multi-antibiotic resistance. The Applicant instead argues that the reference is concerned with the prevention of such multi-antibiotic resistance. However, while the reference is indeed with the development of treatments that avoid the development of drug resistance, the reference teaches that this is performed by the study of the mechanisms leading to drug, including multi-drug, resistance. In order to study such mechanisms, it would have been obvious to those of ordinary skill in the art that one would need access to such multidrug resistant bacteria. In view of these teachings, and those of the other references which cumulatively suggest the creation of bacteria with phenotypes of interest through the introduction

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a mismatch repair defect, it would have been obvious to those in the art to apply such methods for the creation of multidrug resistant bacteria.

The Applicant's arguments with respect to these references individually are therefore not found persuasive, because while no one of the references provides sufficient teachings to render every limitation of the claims obvious, the cumulative teachings of the references are sufficient to establish a prima facie case of obviousness. For these reasons, and for the reasons of record, the rejection is maintained against pending claims 1, 51, 27, and 38.

9. **(Prior Rejection- Withdrawn)** In the prior action, claims 1, 19, 27, and 38 were rejected under 35 U.S.C. 103(a) as being unpatentable over Iris (U.S. Patent 6,221,585) in view of Stemmer (U.S. Pub 2001/0049104) and Johnston (U.S. Patent 6,043,048), in view of Aronshtam et al. (Nucleic Acids Research, 24(13): 2498-2504), and further in view of the teachings of LeClerc (Science 274: 1208-11), Drummond (J Biol Chem, 271: 19645-48), and Moreland (Cancer Research, 59:2102-04), and Morris et al. (J Infect Dis 171: 954-60). The claims have been amended to require that the dominant negative allele of the mismatch repair gene is that of either PMS1-134 or PMSR3. As none of the cited references teach these alleles, the rejection is withdrawn.

10. **(Prior Rejection- Maintained)** Claims 1, 3, 27, 38, and 42 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over Iris in view of Stemmer and Johnston as applied to claims 1, 2, 27, and 38 above, and further in view of either Nicolaides et al., Molecular and Cellular Biology, 18(3): 1635-1641 (Nicolaides 2) or Nicolaides et al., U.S.

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Patent 6,146,894 (Nicolaidis 3) and of LeClerc, Drummond, Moreland, and Morris. Claims 3 and 42 have been cancelled from the application. The rejection is therefore withdrawn from these two claims. The Applicant traverses this rejection on several grounds. First, the Applicant asserts that one of ordinary skill in the art would not have been motivated by the teachings of Iris to create a hypermutable bacteria having randomized mutations. The Examiner agrees that the teachings of this reference alone would not have provided adequate suggestion or motivation to make such bacteria. However, the rejection is not based on only the Iris reference. One cannot overcome a rejection over a combination of references by arguing that one of the cited references does not alone teach or suggest the claimed invention. See, MPEP § 2145 IV. This argument is therefore not found persuasive.

The Applicant next provides arguments relating the teachings of the other cited references. These arguments are substantially the same as those presented in the prior Response with respect to claims 1, 19, 27, and 28. These arguments were previously considered and not found persuasive for the reasons described on pages 8-12 (item 9) in the prior action. It is noted that, in the discussion of the references, the Applicant also asserts that the Morris reference (and the LeClerc reference) fail to provide motivation to create multidrug resistant bacteria, because the references are concerned with the prevention of such multidrug resistance. This argument was considered above with respect to the combination of Nicolaidis I, Iris, and Morris. As indicated above, while the reference is indeed with the development of treatments that avoid the development of drug resistance, the reference teaches that this is performed by the study of the mechanisms leading to drug, including multi-drug, resistance. In order to study such mechanisms, it would have been obvious to those of ordinary skill in the art that one would need

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access to such multidrug resistant bacteria. In view of these teachings, and those of the other references which cumulatively suggest the creation of bacteria with phenotypes of interest through the introduction a mismatch repair defect, it would have been obvious to those in the art to apply such methods for the creation of multidrug resistant bacteria. Thus, this argument is also not found persuasive.

For these reasons, and for the reasons of record, the traversals are not found persuasive, and the rejection is maintained against pending claims 1, 27, and 28.

11. **(Prior Rejection- Maintained)** Claims 1, 3, 14-25, 27, 38, and 42, 43, 45-50 were rejected under 35 U.S.C. 103(a) as being unpatentable over either of 1) Iris, Stemmer, Johnson, in view of Aronshtam; or 2) Iris, Stemmer, Johnston and either or Nicolaides 2 or 3, and in view of LeClerc, Drummond, Moreland, and Morris and further in view of Lin (U.S. Patent 6,025,400, column 1), Chang et al. (U.S. Patent 6,043,220, column 1), Setterstrom et al. (U.S. Patent 6,410,056, column 4), and The Merck Index, (1983, pages 2036, 5032-33, and 6448-449) as presented in the prior action. Claims 3, 42, 45, 49, and 50 have been cancelled from the application. The rejection is therefore withdrawn from these cancelled claims.

The Applicant traverses the rejection for the reasons provided above with respect to claims 1, 27, and 38, and additionally argues that "bacterial resistance to a plurality of antibiotics including those listed in claim 14-25 has not been established," and that therefore there is no motivation or reasonable expectation of success in the making of bacteria multiply resistant to such antibiotics. This argument was made in the prior Response of January 2005. It was not

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found persuasive for the reasons indicated in the prior action. The rejection is therefore maintained for the reasons above and the reasons of record.

12. **(Prior Rejection- Maintained)** Claims 1, 3, 14-25, 27, 38, and 42-50 were rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolaides 1 in view of Iris and Morris as applied against claims 1, 3, 15, 27, 38, and 42 above, and further in view of Stemmer, Lin, Chang, Setterstrom, and The Merck Index. Claims 3, 42, 44, 45, 49, and 50 have been cancelled from the application. The rejection is therefore withdrawn from these cancelled claims. The Applicant traverses this rejection for the reasons indicated with respect to the rejection over Nicolaides 1 in view of Iris and Morris above, and for the reasons indicated with respect to the rejection of item 11 above (i.e. lack of motivation and reasonable expectation of success). These arguments are not found persuasive for the reasons indicated above in items 8 and 11. The rejection is therefore maintained over pending claims 1, 14-25, 27, 38, 43, and 46-48.

13. **(Prior Rejection- Maintained)** Claims 27, 44, and 46 were rejected under 35 U.S.C. 103(a) as being unpatentable over 1) Iris, Stemmer, Johnson, in view of Aronshtam; or 2) Iris, Stemmer, Johnston and either or Nicolaides 2 or 3, and in view of LeClerc, Drummond, Moreland, and Morris, and further in view of Lin, Chang, Setterstrom, and The Merck Index as applied above, and further in view of Nicolaides 1. The Applicant traverses this rejection for "reasons previously described." Because none of the previously described arguments were found persuasive for the reasons above and the reasons of record, the rejection is maintained.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. **(Prior Rejection- Maintained)** Claims 1, 3, 15, 27, 38, and 42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 16, 17, 71, and 73 of copending Application No. 09/780,675 in view of Iris and Morris. The Applicant provides no arguments in traversal of these rejections. While the Applicant requests that these rejections be held in abeyance, it is against Office policy to do so. The rejection is therefore maintained against pending claims 1, 15, 27, and 38.

16. **(Prior Rejection- Maintained)** Claims 1, 3, 14-25, 27, 38, and 42-50 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 16, 17, 71, and 73 of copending Application No. 09/780,675 in view of Iris and Morris as applied against claims 1, 3, 15, 27, 38, and 42 above, and further in view of Stemmer, Lin, Chang, Setterstrom, and The Merck Index. The Applicant provides no arguments in traversal of these rejections. While the Applicant requests that these rejections be held in

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abeyance, it is against Office policy to do so. The rejection is therefore maintained against pending claims 1, 14-25, 27, 38, 43, and 46-48.

Conclusion

17. No claims are allowed.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

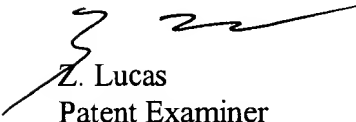
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Z. Lucas
Patent Examiner



JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
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8/8/05